CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
SUMMARY OF TOXICOLOGICAL DATA
TOXICOLOGY BRANCH

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CHLORDANE

SB 950-170, Tolerance #122

January 14, 1987
(Revised 7/31/87)

I. DATA GAP STATUS

Combined rat: Data gap, inadequate study (see "Oncogenicity Rat"), possible adverse e
indicated.

Chronic dog: Data gap, no study on file.

Oncogenicity rat: No data gap, possible adverse effect.
Oncogenicity mouse: No data gap, possible adverse effect.

Reproduction rat: Data gap, inadequate study, no adverse effect indicated.

Teratology rat:Data gap, no study on file.

Teratology rabbit: Data gap, inadequate study, no adverse effect indicated.

Gene mutation: No data gap, possible adverse effect.

Chromosomal aberration: Data gap, inadequate studies, no adverse effect indicated.

DNA damage: Data gap, inadequate studies, no adverse effect indicated.

Neurotoxicity: Not required at this time.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
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II. TOXICOLOGY ONE-LINERS AND DISCUSSION

COMBINATION (CHRONIC + ONCO) RAT: Inadequate study for combined, but is adequate to fill oncogenicity data gap. See "Oncogenicity Rat" below.

CHRONIC RAT

-021, 910031; Title: Albino Rats Subjected to alpha and gamma Chlordane Incorporated the Daily Diet for Two Years; Lab is not clear, 1970; Chlordane (purity not stated) fed diet at 0, 5, 15, 25, 35, 50 and 75 ppm for two years; potential chronic liver effect (liv hypertrophy); potential NOEL for alpha chlordane = 15 ppm, for gamma chlordane = 35 ppm an 1:1 mixture = 25 ppm; UNACCEPTABLE (inadequate number of animals, pathology not included, analysis of dosing material, no justification of dosing levels, intercurrent disease), NOT UPGRADABLE. J.R. Gee, 5/17/85.

-029, 24546; Title: Chronic Oral Toxicity of Oxychlordane in Albino Rats; Velsicol, 1 Chlordane (purity not indicated) given in the diet at 0, 0.05, 1, 5, and 10 ppm for 109 we 50/sex/group; morphological changes in liver at high dose level; no increase in incidence tumors reported; tentative NOEL = 5 ppm; UNACCEPTABLE (no individual animal data, no patho data provided, excessive mortality at high dose level), NOT UPGRADABLE. J.R. Gee, 9/9/85.

-025, 16946: Review of chlordane toxicology. Chronic effects on liver indicated witho clear reference to study of origin.

CHRONIC DOG: No study on file.

ONCOGENICITY RAT

** **-023, 16931**; Title: Thirty-month Chronic Toxicity and Tumorigenicity Test in Rats wit Chlordane Technical; Research Institute for Animal Science in Biochemistry and Toxicology (Japan), 12/1/83; Chlordane (technical, lot B-9129A, 100%); fed in the diet at 0, 1, 5 or (nominal) for 130 weeks; 80/sex/group; oncogenic and chronic effects on liver at high dose level; tentative onco NOEL between 1-5 ppm (nominal), systemic NOEL, not demonstrated; originally reviewed as UNACCEPTABLE as combined study - high mortality, no eye exam, liver disease in males as a complication - (J.R. Gee, 5/21/85); Upgraded to ACCEPTABLE oncogenic study by rebuttal (see -036 below) and second review. F. Martz, 7/31/87.

EPA 1-liner: Supplementary initially but upgraded to minimum. Oncogenic NOEL = 5 p (increased incidence of benign hepatocellular) Systemic NOEL = 1 ppm (increased incidence hepatocellular swelling and hepatocellular necrosis in males).

-036: Rebuttal to 122-023, 16931: "Thirty-month chronic toxicity and tumorogenicity t rats with chlordane technical;" Research Institute for Animal Science in Biochemistry and Toxicology (Japan), 12/1/83; chlordane technical to 80/sex/level with 8/sex/level interim sacrificed at 26 and 52 weeks, with termination at 130 weeks (2.5 years); hepatocellular n ("adenomas") with reduced survival beginning after 116 weeks @ 25 ppm, NOEL between 1-5 pp hepatocellular swelling and necrosis, no NOEL. Upgraded to complete and ACCEPTABLE as an oncogenicity study; not upgradable as a combined study because no ophthalmoscopic exams we done. F. Martz, 7/31/87.

-020, 910028; Title: Bioassay of Chlordane for Possible Carcinogenicity; Gulf South Inst. for NCI, 1977; Chlordane (94.8%) fed in the diet for 80 weeks at 0, 121 (females onl 205.5 (males only), 242 (females only) and 407 (males only) ppm--Time Weighted Averages, f initiated at 200 and 400 ppm, males initiated at 400 and 800 ppm; 10/sex in controls, 50/sex/group in exposure groups; 29 weeks of observation after dosing period; no adverse e reported; UNACCEPTABLE (only two dosing levels, changes in the dosing levels, inadequate n

of controls, inadequate spread of dosing levels, no individual animal data, problem with autolysis of tissues, no tables included), NOT UPGRADABLE. J.R. Gee, 5/24/85.

-026, 16946: Duplicate of 910028 above.

-025, 16936: Review of chlordane toxicity; indicated onco effects on liver of rats an without giving clear reference to study of origin.

ONCOGENICITY MOUSE

-021, 910029; Title: Eighteen Month Oral Carcinogenic Study in Mice; IRDC, 12/73; Chl (technical, 100%, Standard No.: RS-B8113) fed in the diet for 18 months at 0, 5, 25 and 50 to CD-1 mice; 100/sex/group; nodular hyperplasia in the liver at mid and high dose levels; tentative NOEL < 5 ppm; UNACCEPTABLE (survival in high dose group low, no justification of dosing levels, no analysis of dosing material, no hematology, incomplete histopathology da J.R. Gee, 5/17/85.

-027, 16973: Duplicate of 910029 above.

-020, 910028; Title: Bioassay of Chlordane for Possible Carcinogenicity.Gulf South Re Inst. for NCI, 1977; Chlordane (94.8%) fed in the diet for 80 weeks at (Time Weighted Aver 0, 29.9 (males only), 30.1 (females only), 56.2 (males only) and 63.8 ppm (females only), initially exposed to 20 or 40 ppm, females initially exposed to 40 or 80 ppm; 20/sex in controls, 50/sex/group in treated groups; 10 weeks of observation follow exposure; increas incidence of liver carcinomas at all exposure levels; onco NOEL < lower dose (29.9 ppm in 30.1 ppm in females); UNACCEPTABLE (inadequate number of controls, spread of dose levels n adequate, changing of dosing levels, no individual animal data, missing tables), NOT UPGRA J.R. Gee, 5/24/85.

** **-024, 16932**; Title: Twenty-four month Chronic Toxicity and Tumorigenicity Test in Mic Chlordane Technical; Res. Inst. Anim. Sci., Japan--12/1/83; Chlordane (technical, 100%, L 9129A) fed in the diet at 0, 1, 5 and 12.5 ppm for 104 weeks to ICR mice; 80/sex/group; hepatocyte swelling at high and mid dose levels, liver adenomas in males at high dose leve NOEL = 1 ppm; ACCEPTABLE. J.R. Gee, 5/21/85.

EPA 1-liner: Minimum. [Initially reviewed as invalid but upgraded to minimum.] Onc NOEL = 5 ppm (hepatocellular adenomas and hepatic hemangiomas) Systemic NOEL = 1 ppm (hepatocellular swelling and necrosis in males, hepatocyte swelling in males, increased li weight in male and female).

-028, 16974; Naylor Dana Inst., 1984, Journal article; Tumor promotor study; Chlordan (purity not stated) fed in the diet for 25 weeks at 0, 25 and 50 ppm to $B6C3F_1$ mice; males on study; animals exposed to DEN for 14 weeks prior to chlordane exposure; liver neoplasms observed at both dose levels (+ DEN), indicating that chlordane may be promoter; UNACCEPTA for oncogenicity data requirements. J.R. Gee, 5/21/85.

-026, 16950 Title: Carcinogenicity of Heptachlor and Chlordane. Journal article in T Science of the Total Environment, 6: 103-154, S. S. Epstein, Case Western Reserve. Articl discusses FDA (1965), IRDC (1973) and NCI (1975) studies on chlordane; the overall conclu indicates an onco effect of this material.

-017, 12859: Monograph on chlordane toxicity; Summarizes chronic and reproductive eff on chlordane.

-027, 16972; Title: Carcinomas and Other Lesions of the Liver in Mice ingesting Organochlorine Pesticides. Journal article in Toxicology Annual 3: 231-256 (1979), M.D. R General article discussing liver effects of organochlorine pesticides.

-025, 16944: Discussion of chlordane potential oncogenicity effects.

-026, 16949; Title: An Evaluation of the Carcinogenicity of Chlordane and Heptachlor Prepared in October, 1977, by the Pesticide Information Review and Evaluation Committee fo National Research Council, National Academy of Science reviewing the potential carcinogeni effects of chlordane.

REPRODUCTION

-025, 16933; Title: Review of the Toxicology of Chlordane and Heptachlor, Part I: Chlordane. (Velsicol, 1984). Summary of reproduction study with chlordane, conducted in 19 Velsicol; no adverse effect reported; UNACCEPTABLE (need complete report). J.R. Gee, 5/20

-017, 12859: Monograph on chlordane; includes discussion on potential of reproductive effects.

TERATOGENICITY, RAT: No study on file.

TERATOGENICITY, RABBIT

-027, 16965; Title: Teratology Study in Rabbits; IRDC, 5/72; Chlordane (purity not st technical, RS-B8113) given by oral gavage to Dutch belted rabbits at 0, 1, 5 and 15 mg/Kg/ days 6-18 of gestation; 19-20/group; no adverse effects reported; UNACCEPTABLE (intercurre disease resulted in excessive deaths, individual animal data missing, especially for high group, no analysis of dosing solution), NOT UPGRADABLE. J.R.Gee, 5/24/85.

-027, 16966; Title: Pilot Rabbit Teratology Study; IRDC, 12/13/71, Pilot for #16965 Chlordane (technical, same lot), given by oral gavage at 0, 1, 5, 10, 25 or 50 mg/kg/day, 6-18 of gestation; clinical signs at 25 and 50 mg/kg/day.

EPA 1-liner: No CORE grade. Maternal NOEL = 5 mg/kg/day (decreased body weight.)

-025, 16934: Review of chlordane toxicological data, including IRDC teratology study.

GENE MUTATION

Microbial Systems

-021, 910033; Title: In vitro Microbiological Mutagenicity Studies of Six Velsicol Ch Corporation Samples; SRI, 6/77; Chlordane (purity not stated) tested at 0, 10, 50, 100, 50 1000 and 5000 ug/plate on Salmonella strains TA98, 100, 1535, 1537, and 1538 +/- S9; possi increase in mutation frequency in strains TA98, 100, 1535 and 1537; UNACCEPTABLE (question results due to toxicity and ppt of test article, single platings with no repeat trials), N UPGRADABLE. J.R. Gee, 5/20/85.

-026, 16964: Duplicate of record #910033 above.

-026, 16963; Title: Mutagenic Activity of Chemicals Identified in Drinking Water; Publication in Progress in Genetic Toxicology 1977: 249 - 258, V.F. Simon et al, SRI; Rev Ames test on 300 chemicals with no data included; no adverse effects of chlordane reported UNACCEPTABLE, NOT UPGRADABLE. J.R. Gee, 5/22/85.

-026, 16962; Title: Report of Mutagenicity Test; Chem. Inspect. Test. Inst., Japan, 8 Chlordane (technical, 100 %) tested at 0, 5, 10, 50, 100, 500, 1000, 5000 and 10,000 ug/p on Salmonella strains TA98 and 100 +/- S9; possible dose response with technical chlordane no increase mutation frequency with alpha and gamma chlordane; UNACCEPTABLE (no repeat tri only two strains used); NOT UPGRADABLE. J.R. Gee, 5/22/85.

EPA one-liner: Significant increase in the number of revertant colonies per plate for Salmonella typhimurium TA100 but not to TA98; Acceptable.

-026, 16952; Title: An Evaluation of the Genotoxic Properties of Insecticides followi Plant and Animal Activation. Journal article in Mutation Research, 101: 19-29 (1982), J. Gentile et al.; Ten insecticides screened for mutagenicity potential in Salmonella strains 98, 100, 1535, 1537 and 1538; no adverse effects of chlordane noted; UNACCEPTABLE, NOT UPGRADABLE. J.R. Gee, 5/23/85.

-034, 42842; National Toxicology Program, 1/83; Chlordane (no purity indicated) teste Salmonella strains TA98, 100, 1535 and 1537 at 0 to 33 ug/plate without S9 and 100 to 10,0 ug/plate with S9 (rat and hamster liver); no adverse effects reported; summary only with t no text or description of methods; UNACCEPTABLE (need full report), POSSIBLY UPGRADABLE. Gee, 7/25/85.

SUMMARY: Although no single report fulfills all criteria for acceptability, when the available from the several studies are compiled, adequate information exists to fill the d gap.

Mammalian Systems

-026, 16958; Title: Pesticide Induced Ouabain Resistant Mutants in Chinese Hamster V7 Cells. Journal article in Chem. Biol. Interactions, 19: 369-374 (1977); Chlordane tested a and 0.01 mM on Chinese hamster cells (V79) without metabolic activation; increased mutatio frequency reported; UNACCEPTABLE (inadequate dosing range, no S9 used, test article inadeq described, no positive control), NOT UPGRADABLE. J.R. Gee, 5/22/85.

-026, 16957; Title: Rat Hepatocyte-Mediated Mutagenesis of Human Cells by Carcinogeni Polycyclic Aromatic Hydrocarbons but not Organochlorine Pesticides. Journal article in Pr Soc. Exptl. Biol. Med., 167: 572-575 (1981), Naylor Dana Inst.; Chlordane (purity not desc tested at 10^{-4} and 10^{-5} M on human skin fibroblasts; no adverse effects reported; UNACCEPT

(incomplete description of procedures, test article inadequately described, inadequate ran doses, no metabolic activation), NOT UPGRADABLE. J.R. Gee, 5/22/85.

CHROMOSOMAL ABERRATION

-026, 16953; Title: Detection of Chemical Mutagens by the Dominant Lethal Assay in th Mouse. Journal article in Toxicology and Applied Pharmacology 23: 288-325 (1972), S.S. Eps et al from Harvard Med. School; Chlordane (alpha and gamma, no purity reported) given by gavage at 75 mg/Kg or by i.p. injection at 42, 58, 210 and 290 mg/Kg to ICR/Ha Swiss mice dominant-lethal assay; 7-10 males/group; mated with 3 females/week for 8 weeks; no adverse effects reported; UNACCEPTABLE (inadequate number of animals, several other major variatio from guidelines), NOT UPGRADABLE. J.R. GEE, 5/23/85.

-026, 16954; Title: Dominant Lethal Studies with Technical Chlordane, HCS-3260, and Heptachlor: Heptachlor Epoxide. Journal article in J. Toxicology and Environmental Health 547-555 (1977), D.W. Arnold et al, IBT, 77 (Valid ??); Chlordane (mixture of isomers, heptachlor and other compounds) tested on CD-1 mice for dominant-lethal assay at 0, 50, or mg/kg by oral gavage or by i.p. injection; 8 males/group; mated over 6 weekly periods at 1 adverse effect reported; UNACCEPTABLE (inappropriate test material, inadequate number of animals, no individual animal data, no positive control, several other deviations from guidelines), NOT UPGRADABLE. J.R.Gee, 5/23/85 and re-reviewed 7/29/86.

EPA status unknown.

-034, 42645: Supplement to record #16954 above.

-035, 46796; Title: Chromosomal Aberration in CHO Cells; Litton, 4/2/86; Chlordane, n purity stated; tested at 17.0, 18.0 or 20.0 ug/ml without activation, 20.5 hours, and 24.9 27.0, 30.1 or 33.2 ug/ml with rat liver activation for 2 hours followed by further incubat for a total of 21.0 hours for chromosomal aberrations; for the sister chromatid exchanges,

without activation, tested at 5.0 ug/ml in trial 1 and at 7, 10, 13 or 14 ug/ml in trial 2 with rat liver activation, tested at 16.7 ug/ml in trial 1 and at 20.1, 24.9, 30 or 35 ug/ trial 2; general protocol (1 page) submitted with data indicated cells for SCE's were incu with test compound for 26 hours in the absence of activation and for 2 hours with S9 prese unacceptable (report is not complete - need purity of test article, more details of actual test). No evidence of increase in chromosomal aberrations or sister chromatic exchanges u the conditions of the test. J.R.Gee, 11/12/86.

DNA DAMAGE

-026, 16960; Title: Mutagenicity of Dichlorvos; Journal article in Nature 240: 40-41 (1972), M. J. Ashwood-Smith et al, Univ. Victoria; Chlordane (60% with 40% related compou and several other pesticides tested on E. coli (WP2); no data presented; no adverse effect reported; UNACCEPTABLE, NOT UPGRADABLE. J.R. Gee, 5/22/85.

-026, 46902; Title: An Evaluation of the Genotoxic Properties of Insecticides Followi Plant and Animal Activation; Journal article in Mutation Research 101: 19-29 (1982), J.M. Gentile et al.; Chlordane (no purity given) tested at 33 ug on Saccharomyces(D4); positive response +S9 in ade 2 and trp 5 loci; UNACCEPTABLE (only one dose level, no description of article, several other major variances from guidelines), NOT UPGRADABLE. J.R. Gee, 5/23/8

-027, 16971; Title: Tumor Promoting Epigenetic Effects on Liver Cell Membranes by Nongenotoxic Organochlorine Pesticides. Lab ??, date ?, report by S. Telang et al.; Chlord (no purity stated) tested at 10^{-3}, 10^{-4} and 10^{-6} M on primary rat (Fischer 344) hepatocyte adverse effects noted; UNACCEPTABLE (no description of test article, incomplete descriptio procedures, figures missing), POSSIBLY UPGRADABLE. J.R. Gee, 5/24/85.

-021, 910027; Title: Liver Cell Culture Systems for the Study of Hepatocarcinogenesis Naylor Dana Inst., 10/78; Journal article. Chlordane (no purity given) tested on rat hepatocytes; table and commentary suggest a possible slight positive effect with chlordane $HGPRT^-$ mutation, but lack of protocol details renders a judgment impossible; UNACCEPTABLE, UPGRADABLE. J.R. Gee, 5/17/85.

-026, 16955; Title: Evidence for an Epigenetic Mode of Action in Organochlorine Pesti Hepatocarcinogenicity: A Lack of Genotoxicity in Rat, Mouse and Hamster Hepatocytes; Journ article in J. Toxicology Environmental Health, 8: 121-130 (1981), C.J. Maslansky and G.M. Williams, N.Y. Med College; Chlordane (no description of test article) tested at 10^{-4} M o mouse and hamster hepatocytes; no adverse effects reported; UNACCEPTABLE (only a single do level tested, test article not characterized, inadequate number of cells, other major vari from guidelines), NOT UPGRADABLE. J.R. Gee, 5/23/85.

-026, 16956; Title: Pesticide Induced DNA Damage and its Repair in Cultured Human Cel Journal article in Mutation Research 42: 161-174 (1977), F. E. Ahmed et al., Ohio St. Univ Chlordane (purity not indicated) tested at 0, 1, 10, 100 and 1000 uM +/- S9 on human fibro (VA-4) in UDS assay; Chlordane induced UDS at 1 to 1000 uM without S9, but not in presence S9; UNACCEPTABLE (no positive controls, test article not defined, no toxicity data, counte few nuclei, no justification of dose levels), NOT UPGRADABLE. J.R. Gee, 5/23/85.

-025, 16942: Discussion of UDS potential of chlordane.

-035, 46796: Sister Chromatid Exchange in Chinese Hamster Ovary Cells. See under Mutagenicity, Chromosomes, above.

GENERAL

-025, 16935: General discussion of mutagenicity studies with chlordane.

-019, 910063: EPA risk/benefit analysis of pesticides used for termite control (chlor included).

-035, 46797: Comments by D. Brusick, 5/83. Discussion of the published literature on genotoxicity arguing that chlordane is nonmutagenic but a promoter.

-037, 54443: EPA Registration Standard for chlordane, 12/31/86.

NEUROTOXICITY: Not required.

FILENAME: SB170CHL.JG2
REVISION DATE: 7/31/87, Rebuttal to combined rat with status change to oncogenicity r added, see -023, 16931; and -036.